Prognostic models for 9 month mortality in tuberculous meningitis

Le Thi Phuong Thao[1], A. Dorothee Heemskerk[1,2], Ronald B. Geskus[1,2], Nguyen Thi Hoang Mai[3], Dang Thi Minh Ha[4], Tran Thi Hong Chau[1], Nguyen Hoan Phu[3], Nguyen Van Vinh Chau[3], Maxine Caws[1,5], Nguyen Huu Lan[4], Do Dang Anh Thu[3], Nguyen Thuy Thuong Thuong[1], Jeremy Day[1,2], Jeremy J. Farrar[1,2], M. Estee Torok[6], Nguyen Duc Bang[4], Guy E. Thwaites[1,2], Marcel Wolbers[1]

Affiliation: 1. Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam, 2. Nuffield Department of Medicine, University of Oxford, United Kingdom, 3. Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam, 4. Pham Ngoc Thach Hospital, Ho Chi Minh City, Viet Nam, 5. Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, United Kingdom, 6. Department of Medicine, University of Cambridge, United Kingdom.

Corresponding authors**:**

Guy E. Thwaites, Oxford University Clinical Research Unit, 764 Vo Van Kiet, Quan 5, Ho Chi Minh City, Vietnam. Tel: +84 8 39237954, email: gthwaites@oucru.org

Summary: We developed and validated prognostic models, using data from 1699 HIV-uninfected and HIV-infected adults with tuberculous meningitis (TBM). The final models showed good performance, and could be used in clinical practice to identify TBM patients at high risk of death.

Abstract

Background: Tuberculous meningitis (TBM) is the most severe form of extra-pulmonary tuberculosis. We developed and validated prognostic models for 9-month mortality in HIV-uninfected and HIV-infected adults with TBM.

Methods: We included 1699 subjects from four randomized clinical trials and one prospective observational study conducted at two major referral hospitals in Southern Vietnam from 2001-2015. Modelling was based on multivariable Cox proportional hazards regression. The final prognostic models were validated internally and temporally, and displayed using nomograms and a web-based app (https://thaole.shinyapps.io/tbmapp/).

Results: A total of 951 HIV-uninfected and 748 HIV-infected subjects with TBM were included, of whom 219/951 (23.0%) and 384/748 (51.3%) died during 9-month follow-up. Common predictors for increased mortality in both populations were higher Medical Research Council (MRC) disease severity grade and lower cerebrospinal fluid lymphocyte cells count. In HIV-uninfected subjects, older age, previous tuberculosis, not receiving adjunctive dexamethasone, and focal neurological signs were additional risk factors; in HIV-infected subjects, lower weight, lower peripheral blood CD4 cell count, and abnormal plasma sodium were additional risk factors. The areas under the receiver operating characteristic curves (AUCs) for the final prognostic models were 0.77 (HIV-uninfected population) and 0.78 (HIV-infected population), demonstrating markedly better discrimination than the MRC grade (AUC 0.66 and 0.70) or the Glasgow Coma Score (AUC 0.68 and 0.71) alone.

Conclusions: The developed models showed good performance and could be used in clinical practice to assist doctors in identifying TBM patients at high risk of death and at increased need of supportive care.

Keywords: Tuberculous meningitis; prognostic models; mortality; HIV

Introduction

Tuberculous meningitis (TBM) accounted for around 1-5% of the 10.4 million new tuberculosis cases in 2015 and is the most severe manifestation of the disease, killing or disabling around half of all sufferers [1] . TBM is especially common in children and those infected with HIV, in whom outcomes are poor [2]. In a recent trial conducted in Vietnam, approximately 30% of the participants died during the 9-month study period and 40% of the survivors had disabilities [3].

The British Medical Research Council (MRC) constructed the first TBM severity grades for use in the 1948 trial of streptomycin [4]. Patients were sub-divided based on clinical experience rather than statistical derivation into 'early' (no clinical signs of meningitis or focal neurology and fully conscious), 'medium' (patient's condition falling between early and advanced) and 'advanced' (extremely ill, in deep coma). With the introduction of the Glasgow coma score (GCS) in 1974, this was modified to: Grade I (GCS 15; no focal neurological signs), Grade II (GCS 11-14, or 15 with focal neurological signs) and Grade III (GCS≤10)[5]. This grading system has become the most widely used classification for TBM severity. Despite the age of the MRC scale, and its lack of statistical derivation, improved and robust prediction models for poor outcomes (mortality and/or neurological deficit) in TBM based on large cohort studies and rigorous statistical methodology are still lacking. Amongst prognostic studies in TBM published in the last 20 years, the majority were based on a small number of subjects (from 23 - 507), and modern prognostic modelling tools for handling missing data or model validation were rarely used [6–9].

The primary objective of this study was to develop and validate novel robust prognostic models for 9-month mortality in adult TBM patients with and without HIV co-infection. The models were based on a large dataset of 1699 subjects (951 HIV-uninfected, 748 HIV-infected) enrolled in four randomized controlled trials and one prospective cohort study conducted in Vietnam. In addition, we compared the predictive performance of the developed models with the MRC grading system and the GCS, both widely used in the assessment of TBM severity.

Methods

Study population

Study participants: The study population comprised subjects enrolled in five TBM studies conducted between 2001 and 2015 at two tertiary referral centers in Ho Chi Minh City, Vietnam: Pham Ngoc Thach (PNT) Hospital and the Hospital for Tropical Disease (HTD) [3,10–13].

Detailed descriptions of the studies have been published elsewhere [3,10–13] and are summarised in Supplementary Table 1. All studies were approved by the Oxford Tropical Research Ethics Committee, and the HTD and PNT Hospital Ethics Committees.

Inclusion criteria: The inclusion criteria for the five studies are provided in Supplementary Table 1. In brief, all five studies included adult subjects with a clinical diagnosis of TBM defined as having more than 5 days of meningitis symptoms, nuchal rigidity, and CSF abnormalities suggestive of TBM; additional criteria were radiological evidence of TB on chest X-ray or brain scan, or microbiological evidence of TB from specimens other than CSF. Diagnostic categories of definite, probable, or possible TBM were defined according to study-specific diagnostic criteria as the uniform TBM case definition only became available in 2010 [14]. All study participants were included in the pooled analysis except if they had a confirmed alternative diagnosis, a study drug administration error, or an unknown HIV status.

Laboratory investigation: CSF specimens were stained and cultured by standard methods for pyogenic bacteria, mycobacteria, and fungi. In the last study [3], CSF was additionally tested with the Xpert MTB/RIF assay (Cepheid, California, USA). Isolates of *M. tuberculosis* were tested for susceptibility to isoniazid, rifampin, ethambutol, and streptomycin by the mycobacterial growth indicator tube method [15]. Baseline peripheral blood CD4 cell counts were measured for all HIV-infected adults by flow cytometry.

Anti-tuberculosis and adjunctive treatment: Unless study participants were randomized to an experimental anti-tuberculosis treatment, participants received standard anti-tuberculosis regimen consisting of isoniazid (5mg/kg/day; maximum 300mg/day), rifampin (10mg/kg/day; maximum 600mg/day), pyrazinamide (25mg/kg/day; maximum 2g/day) and ethambutol (20mg/kg/day; maximum 1.2g/day) or streptomycin (20mg/kg/day; maximum 1g/day) for 3 months, followed by rifampin and isoniazid at the same doses for a further 6 months. Since 2005, all patients received adjunctive dexamethasone for the first 6-8 weeks of treatment [3].

Primary outcome

The primary endpoint was overall survival during a 9-month follow-up period. Patients without documented death during the follow-up period were censored at 9 months or at the last date they were known to be alive, whichever was earlier.

Candidate predictors

Candidate predictors were initially selected based on clinical judgement, their status as established risk factors in previous publications [6–9,16–18], and completeness of the data. The number of predictors was further restricted based on a rule of thumb of requiring at least 10 events for each included predictor variable or degree of freedom [19]. The final list of candidate predictors is presented in Supplementary Table 2. For all laboratory parameters and radiology assessments, we used the value recorded closest to enrolment (up to ± 7 days from enrolment). Of note, CSF total white cell count and CSF total lymphocyte count were strongly correlated; therefore only CSF lymphocyte count was included as candidate predictor. Resistance is known to be an important independent predictor for mortality in subjects with TBM [20,21]. However, unless earlier isolates are available or rapid molecular tests performed, information about a patients' TB drug susceptibility is not available at enrolment. The main models therefore did not include resistance but models with resistance were depicted in the supplementary material. The cohort variable was included in the full model to represent the change in patient management, treatment, and standard of health care over the 15 years' time span of the included studies.

We decided to construct separate prognostic models for the HIV-uninfected and HIV-infected TBM populations because they are clinically distinct populations, and we expected that predictors may differ between them.

Statistical analysis

Full details of the statistical analysis are described in Supplementary appendix S1. In brief, incomplete data were multiply imputed using multivariable imputation by chained equations (mice) [22]. The statistical model of choice was multivariable Cox proportional hazards regression including all pre-specified candidate predictors. We tested for potential non-linear effects of continuous candidate predictors and for interactions, i.e. effect modifications, between age and other candidate predictors. Two variable selection methods were used to simplify the model: i) backwards stepwise selection with a

stopping rule based on Akaike's information criterion, and ii) the Least Absolute Shrinkage and Selection Operator (lasso) [23]. We combined model selection with bootstrapping and based the final models on the most frequently (≥ 60%) included variables across all imputed and bootstrap data sets [24]. We used the area under the cumulative/dynamic ROC curve (AUC) [25] for mortality prediction at 9 months to assess the discrimination of the models and calibration plots [26] to visually assess how closely the predicted mortalities agree with the observed mortalities. Internal bootstrap validation was performed to correct measures of model performance for over-fitting. In addition, we performed temporal validation where data from the most recent trial served as the test dataset to validate models that were developed based on earlier studies. The final prognostic models, i.e. the variable-selected models with the highest AUC, were implemented in a web based mortality calculator and graphically depicted using nomograms [26]. All analyses were conducted using R version 3.3.1 [27].

Results

Baseline characteristics of study participants

The five studies included a total of 1734 subjects, of which 1699 were included for prognostic modelling (Supplementary Figure 1). The reasons for excluding 35 subjects were a confirmed other diagnosis (n = 16), unknown HIV status (n=16), or a study drug administration error (n = 3).

Table 1 presents the baseline characteristics of all included subjects; 951 were HIV-uninfected (56.0%) and 748 (44.0%) were HIV-infected. The median age was 34 years (inter-quartile range 27-45) and 823 (48.4%) had definite, microbiologically confirmed TBM. MRC grade was I in 588 (34.6%) subjects, II in 743 (43.8%) subjects, and III in 367 (21.6%) subjects. Amongst HIV-infected subjects, the median CD4 cell count was 41 cells/mm^3, and 124 (16.6%) were on ART at baseline. Compared with HIV-uninfected subjects, those infected with HIV tended to be younger (median 31 vs. 40 years), were more frequently male (85.6% male vs. 62.3% male) and diagnosed with MRC grade III (25.6% vs. 18.5%).

During 9-month follow-up, 219/951 (23.0%) HIV-uninfected and 384/748 (51.3%) HIV-infected subjects with TBM died. Amongst the 1096 survivors, 998 (91.1%) were followed up for at least 260 days. Yearly recruitment into the five studies and observed mortality by HIV status are shown in Figure 1. The figure displays a decline in mortality over time, which is particularly pronounced in HIV-infected subjects. In this sub-population, the estimated 9-month mortality dropped from 52-92% during 2001-2007 to 35-

50% during 2011-2015. Coincidently, the number of study participant on ART at enrolment in the first period was only 7/407 (1.7%), and increased to 117/341 (34.3%) in the second period.

Prognostic models

Univariable analyses of the effect of all candidate predictors for survival are shown in Supplementary Tables 3 and 4. Results of the multivariable analyses are shown in Table 2 and Supplementary Table 5.

The final models identified a higher Medical Research Council (MRC) disease severity grade and lower cerebrospinal fluid lymphocyte cell counts as risk factors for mortality in both HIV-uninfected and HIV-infected subjects (Table 2). Importantly, the mortality rate in MRC grade III (GCS≤10) was three-fold higher in HIV-uninfected patients and four-fold higher in HIV-infected patients compared to MRC grade I (GCS 15; no focal neurological signs). Mortality for MRC grade II (GCS 11-14, or 15 with focal neurological signs) was intermediate in both populations.

In HIV-uninfected subjects, older age, previous tuberculosis, not receiving adjunctive dexamethasone, and focal neurological signs were additional predictors of higher mortality. Of note, the mortality rate was increased by more than 50% in patients with previous tuberculosis and those with focal neurological signs, and almost doubled for patients who did not receive dexamethasone.

In the HIV-infected population, lower weight, lower peripheral blood CD4 cell count, and abnormal plasma sodium were additional predictors of higher mortality. Plasma sodium had a significant non-linear association with survival, and both decreased and elevated sodium values were associated with a higher predicted mortality compared to intermediate value. Ongoing ART therapy at enrolment was associated with a more favourable outcome in univariable analysis (Supplementary Table 4), but was no longer significantly associated with survival after adjusting for other factors.

There was no clear evidence that age modified the effect of any of the other predictors (p-value for overall interaction test of 0.14 in HIV-uninfected, and of 0.10 in HIV-infected subjects).

Model validation

The final models showed good discrimination between TBM survivors and deaths at 9 months; the corresponding AUCs in internal validation (corrected for over-fitting) were 0.77 in the HIV-uninfected

population and 0.78 in the HIV-infected population, respectively (Table 3). The addition of drug resistance as a covariate resulted in only a slightly improved model discrimination with AUC values ranging from 0.77–0.79 (Supplementary Table 7).

In internal validation, the models showed good agreement between predicted and observed mortality (Supplementary Figures 2a and 2c). In temporal validation, calibration in the HIV-uninfected groups remained satisfactory whereas in the HIV infected group, models developed on earlier studies systematically overestimated the actual mortality in the most recent trial (Supplementary Figures 2b and 2d).

Figure 2 shows predicted survival curves of the final simplified models in four risk groups defined using cut-off points at the 16^{th}, 50^{th}, 84^{th} percentiles of the prognostic index generated by these models [28]. They show strong prognostic separation across risk strata, good agreement between predicted survival curves and Kaplan-Meier estimates in the full dataset, and mild to substantial risk overestimation in temporal validation in HIV-uninfected and HIV-infected subjects

Comparison of prognostic models with MRC grade and GCS alone

MRC grade and GCS predicted mortality similarly well (AUC ranging from 0.66-0.71) (Table 3). The corresponding ROC curves for the MRC grade, GCS and the final models are shown in Figure 3. MRC grade and GCS were both clearly inferior to the developed multivariable models in terms of discrimination (p-values for tests of equality between AUC values <0.001 for all comparisons) whereas discrimination did not differ significantly between MRC grade and GCS (p-value = 0.23 in HIV uninfected and p-value = 0.19 in HIV infected).

Nomograms and web app for mortality prediction

Figure 4 visualizes the final models as nomograms. For clinical use, this model has also been implemented as a user-friendly web app available at https://thaole.shinyapps.io/tbmapp/ . We also generated nomograms for use when resistance information is available (Supplementary Figure 3). Of note, for creation of the nomogram and the web app in the HIV-infected population, the cohort variable was chosen as our most recent trial [3] since this is most relevant for future prediction.

Discussion

We developed and validated prognostic models for 9-month mortality after TBM diagnosis in a large dataset of 951 HIV-uninfected and 748 HIV-infected TBM patients. We found that a higher MRC grade and lower CSF lymphocyte cell counts were predictors for mortality in both groups. MRC grade assesses the severity of neurological impairment and numerous studies have shown its strong association with poor outcome [29,30]. The predictive value of lower CSF lymphocyte counts is intriguing. Others have recently found higher CSF neutrophils predicted death from TBM [31] ; both findings reflect the poorly understood importance of neuro-inflammation to outcome from TBM.

Additional risk factors in HIV-uninfected patients were older age, previous TB treatment, not receiving dexamethasone, and having focal neurological signs. In HIV-infected subjects, additional risk factors for mortality were lower weight, lower CD4 cell count, and abnormal plasma sodium level. These finding are consistent with results from previous published studied conducted in India [32], Hong Kong [17], Taiwan [8], Turkey [33], South Africa [34], and Brazil [35]. The inclusion of different predictors in the two HIV populations may suggest important differences in disease pathogenesis and outcomes in these two subgroups.

The main analysis did not include drug-resistance as a covariate because this information is often not available at enrolment. Alternative models including drug resistance showed only relatively little improvement in model performance, especially in HIV-uninfected subjects. However, we note the low prevalence of multidrug resistant TB (MDR-TB), an important predictor of poor outcome in TBM [20,21], in our cohort which may have contributed to this finding.

The final prediction models were carefully developed and validated with proper statistical methods [36]. They showed good discrimination between TBM-survivors and deaths in both internal and temporal validation, and substantially improved over the MRC grade or the GCS alone. Although our models had excellent calibration in internal validation, they over-estimated mortality in temporal validation where the model was developed on earlier studies and tested on subjects included in the most recent trial. This overestimation was mild in HIV-uninfected subjects but substantial in HIV-infected subjects. It may be explained by improvements in treatment, especially the availability of ART, and patients' supportive care over time. Importantly, because ART only became widely available in Vietnam in 2005 [37] and being on ART was an exclusion criterion for the ART timing trial, the intensified treatment trial [3] was the only study that included subjects on ART at TBM diagnosis. Therefore, the effect of ART was neglected in the

temporal validation, and this may have contributed to the observed overestimation. Temporal heterogeneity was addressed by including the cohort as a covariate in the statistical regression models. Survival for future patients is anticipated to be close to predictions adjusted to our most recent study.

Our study has several limitations, mostly owing to the characteristics of our database. Firstly, CSF lactate, which may be an important risk factor [38], was not taken into account in our final model because it was missing in >40% of subjects. Secondly, previous studies suggested that leukotriene A4 hydrolase (LTA4H) genotype is a determinant of the inflammatory response in HIV-uninfected adults with TBM, and consequently might predict who benefits from adjunctive corticosteroid treatment[39]. This factor, therefore, might have an influence on survival of HIV-uninfected TBM subjects. As the information of LTA4H genotype was not available for all included studies, we did not consider this covariate in our analyses. Thirdly, the models were developed and validated based on data from two large hospitals in Southern Vietnam only. Thus, it would be desirable to validate and possibly improve our models in an independent external database. Finally, our models only included risk factors available at TBM diagnosis. However, changes in biomarkers that are repeatedly measured during the disease course may carry important information which could allow updating and improving an initial prognosis during TB treatment. The value of such longitudinally measured biomarkers will be examined in a future research project.

Our final models were displayed as nomograms and implemented in a user friendly web based risk calculator (https://thaole.shinyapps.io/tbmapp/) for use in clinical practice to improve prognostic stratification in TBM patients. Patients at high risks could be identified early and then put on stricter monitoring schemes to receive appropriate counselling/supportive care, or enrolled in future clinical trials that explore novel treatments targeted to severe TBM.

Our models are based on one of the largest sources of prospectively collected clinical data for TBM disease worldwide. The final prognostic models included variables which are usually available for patients with TBM. Overall, our prediction models have good discrimination and calibration performance, and clearly outperformed the MRC grading score.

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Conflict of interest: none to declare

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Table 1: Baseline characteristics of patients included in the pooled database, overall and by HIV status

Characteristic	All TBM patients (N=1699)		HIV-uninfected TBM (N=951)		HIV-infected TBM (N=748)	
	n	Summary statistic	n	Summary statistic	n	Summary statistic
Cohort	1699		951		748	
- Dexamethasone trial		534(31.4%)		436(45.9%)		98(13.1%)
- Fluoroquinolone trial		56(3.3%)		53(5.6%)		3(0.4%)
- TBM HIV cohort		58(3.4%)		0(0%)		58(7.7%)
- ART timing trial		248(14.6%)		0(0%)		248(33.2%)
- Intensified treatment trial		803(47.3%)		462(48.6%)		341(45.6%)
Age [years]	1698	34(27,45)	951	40(27,56)	747	31(26,35)
Sex: Female	1699	514(30.25%)	951	406(42.7%)	748	108(14.4%)
Weight [kg]	1695	46(41,51)	951	46(42,52)	744	45(40,50)
Dexamethasone treatment: Yes	1699	1436(84.5%)	951	742(78.0%)	748	694(92.8 %)
On ART at enrolment: Yes	745	124(16.6%)	-	-	745	124(16.6%)
MRC Grade §	1698		951		747	
- MRC Grade I		588(34.6%)		327(34.4%)		261(34.9%)
- MRC Grade II		743(43.8%)		448(47.1%)		295(39.5%)
- MRC Grade III		367(21.6%)		176(18.5%)		191(25.6%)
Illness duration at study entry [days]	1685	15(10,30)	948	15(10,26)	737	15(9,30)
Previous TB treatment: Yes	1658	236(14.2%)	922	88(9.5%)	736	148(20.1%)
Focal neurological signs: Yes	1683	818(48.6%)	951	517(54.4%)	732	301(41.1%)
Temperature [degrees Celsius]	1697	37.6(37.2,38.5)	950	37.7(37.2,38.5)	747	37.5(37.2,38.5)
Convulsions: Yes	1685	50(3.0%)	950	25(2.6%)	735	25(3.4%)

Plasma sodium [mmol/l]	1537	129(124,133)	843	130(125,134)	694	127(123,132)
CSF lymphocyte count [cells/ mm^3]	1614	85(27.6,197.5)	919	94(32.5,200)	695	73 (23.3,188.8)
CSF protein [g/l]	1624	1.3(0.70,1.94)	909	1.2 (0.7,2.0)	715	1.3(0.7,1.9)
CSF glucose [mmol/l]	1636	1.60(1.05,2.30)	920	1.52(1.00,2.30)	716	1.70(1.17,2.33)
Ratio of CSF glucose and blood glucose	1470	0.30(0.21,0.41)	830	0.30(0.20,0.40)	640	0.30(0.21,0.42)
Microbiologically confirmed/definite TBM	1699	823(48.4%)	951	361(38.0%)	748	462(61.8%)
Resistance £	1699		951		748	
- No isoniazid or rifampin resistance		479(28.2%)		203(21.4%)		276(36.9%)
- Isoniazid monoresistance		172(10.1%)		63(6.6%)		109(14.6%)
- Rifampin monoresistance /MDR		35(2.1%)		10(1.1%)		25(3.3%)
- Unknown resistance		1013(59.6%)		675(71.0%)		338(45.2%)
Chest x-ray miliary TB: Yes	1525	279(18.3%)	890	165(18.5%)	635	114(17.9%)
Peripheral blood CD4 count [cells/mm^3]	646	41 (16,108)	-	-	646	41(16,108)

Summary statistics are frequency (%) for categorical variables and median (interquartile range, IQR) for continuous variables. n refers to the number of subjects with non-missing data for the respective characteristic.

£: Isoniazid monoresistance is defined as resistance to isoniazid but not to rifampin. Multidrug resistance (MDR) is defined as resistance to at least isoniazid and rifampin. Unknown resistance is defined as drug-susceptibility test results not available. In all categories, resistance to other drugs may be present.

§ MRC Grade I (GCS 15; no focal neurological signs); MRC Grade II (GCS 11-14, or 15 with focal neurological signs); MRC Grade III (GCS≤10)).

Table 2: Final Cox regression models for 9-month survival in each HIV population. Estimates were pooled across multiply imputed datasets.

Variable	HIV-uninfected TBM population						HIV-infected TBM population					
	Full model			Final model (Model selected by the lasso)			Full model			Final model (Model selected by stepwise backwards model selection)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age [per +10 years]	1.24	1.15 - 1.34	<0.001	1.24	1.15 - 1.34	<0.001	0.99	0.85 - 1.16	0.89			
Sex: male	1.07	0.79 - 1.44	0.67				0.95	0.70 - 1.30	0.77			
Weight [per +10 kgs]	0.88	0.73 - 1.06	0.17				0.72	0.61 - 0.85	<0.001	0.73	0.63 - 0.85	<0.001
MRC Grade §												
- MRC Grade I	1			1			1			1		
- MRC Grade II	1.36	0.87 - 2.13	0.17	1.41	0.9 - 2.19	0.13	1.71	1.24 - 2.35	0.001	1.88	1.43 - 2.48	<0.001
- MRC Grade III	2.97	1.83 - 4.83	<0.001	3.05	1.92 - 4.86	<0.001	3.76	2.69 - 5.26	<0.001	4.08	3.07 - 5.41	<0.001
Illness duration at study entry [days] ‡	1.03	0.91 - 1.17	0.61				1.02	0.93 - 1.11	0.73			
Previous TB treatment : Yes	1.46	1.00 - 2.13	0.05	1.57	1.09 - 2.26	0.015	1.26	0.97 - 1.65	0.09			
Focal neurological signs: Yes	1.80	1.22 - 2.64	0.003	1.65	1.15 - 2.39	0.007	1.15	0.87 - 1.53	0.33			
Temperature[Celsius]	0.96	0.79 - 1.17	0.71				1.09	0.96 - 1.24	0.18			
Convulsion: Yes	0.96	0.41 - 2.22	0.92				0.95	0.58 - 1.56	0.83			
Dexamethasone: No	1.67	1.15 - 2.40	0.006	1.97	1.46 - 2.67	<0.001	1.12	0.68 - 1.85	0.65			
Plasma sodium [per +10 mmol/l] £	1.01	0.85 - 1.21	0.89						<0.001			<0.001
- 135 vs. 125	1.01	0.85 - 1.21					1.09	0.91 - 1.31		1.07	0.90 - 1.28	
- 115 vs. 125	0.99	0.83 - 1.17					1.63	1.31 - 2.04		1.06	1.29 - 2.00	
CSF lymphocyte count [cells/ mm^3] ‡	0.88	0.82 - 0.94	<0.001	0.86	0.81 - 0.92	<0.001	0.93	0.87 - 0.99	0.017	0.93	0.88 - 0.98	0.004
CSF protein [g/l] ‡	0.95	0.84 - 1.07	0.38				0.95	0.85 - 1.06	0.37			
CSF glucose [mmol/l]	1.03	0.87 - 1.23	0.70				1.08	0.98 - 1.19	0.10			
Ratio of CSF glucose and blood glucose ‡	1.02	0.81 - 1.28	0.88				0.91	0.77 - 1.08	0.30			
Chest x-ray miliary TB: Yes	0.82	0.56 - 1.18	0.29				0.95	0.70 - 1.29	0.73			
Peripheral blood CD4 [cells/ mm^3] ‡	-	-	-				0.91	0.85 - 0.98	0.012	0.9	0.84 - 0.96	0.002
On ART at enrolment [Yes]	-	-	-				0.87	0.60 - 1.26	0.45			

Cohort									
- Intensified trial	1			1			1		
- Dexamethasone trial	1.46	0.94 - 2.27	0.09	1.96	1.23 - 3.14	0.005	1.72	1.25 - 2.37	<0.001
- Fluoroquinolone trial	1.12	0.51 - 2.46	0.77						
- TBM HIV cohort				2.58	1.63 - 4.06	<0.001	2.64	1.81 - 3.84	<0.001
- ART timing trial				1.78	1.28 - 2.47	<0.001	1.71	1.34 - 2.19	<0.001

HR=hazard ratio, CI=confidence interval. 95% CI and p-value for final models do not take into account the uncertainty of model selection.
‡HR per 2-fold increase.
£ In HIV-infected subjects, the effect of sodium on mortality was significantly non-linear and modelled with a restricted cubic spline function with 2 degrees of freedom. To simplify interpretation of the corresponding regression coefficients, only HRs for two derived sodium contrasts from that model are given. P-values for sodium In the HIV-infected population are based on overall Wald-tests of the restricted cubic spline function
§ MRC Grade I (GCS 15; no focal neurological signs); MRC Grade II (GCS 11-14, or 15 with focal neurological signs); MRC Grade III (GCS≤10)).

Table 3: Discrimination of candidate models for TBM mortality by HIV population measured by the area under the cumulative/dynamic ROC curve (AUC) at 9-months.

Model	Internal validation		Temporal validation
	Apparent AUC (95% CI)*	Optimism Corrected AUC ‡	AUC (95% CI)
HIV-uninfected population			
Full model	0.79 (0.76-0.83)	0.76	0.77 (0.72-0.83)
Model selected by stepwise backwards model selection	0.78 (0.74-0.81)	0.76	0.77 (0.71-0.82)
Model selected by the lasso method **	0.78 (0.75-0.82)	0.77	0.82 (0.77-0.87)
MRC Grade §	0.66 (0.62-0.70)	0.66	0.70 (0.64-0.75)
GCS	0.68 (0.64-0.72)	0.68	0.68 (0.62-0.75)
HIV-infected population			
Full model	0.79 (0.75-0.83)	0.77	0.76 (0.70-0.82)
Model selected by stepwise backwards model selection **	0.79 (0.75-0.82)	0.78	0.73 (0.67-0.79)
Model selected by the lasso method	0.78 (0.74-0.82)	0.77	0.75 (0.69-0.81)
MRC Grade §	0.70 (0.66-0.74)	0.70	0.69 (0.63-0.75)
GCS	0.71 (0.67-0.75)	0.71	0.68 (0.62-0.74)

CI: confidence interval

*Refers to performance estimated directly from the original 45 imputed datasets that were used to develop the prediction models.

‡ Adjusted performance corrected for over-optimism through internal bootstrap validation.

** Final simplified model.

§ MRC Grade I (GCS 15; no focal neurological signs); MRC Grade II (GCS 11-14, or 15 with focal neurological signs); MRC Grade III (GCS≤10)).

Figure legends

Figure 1: Annual recruitment into the five contributing studies by HIV status. The black lines show estimated 9-month mortality (in %) for each calendar year based on the Kaplan-Meier method.

Figure 2: Comparison between predicted survival of the final models and observed Kaplan-Meier estimates. Risk groups are defined using cut-points at the 16th, 50th, 84th percentiles of the prognostic index as generated by the final models (defining "good", "fairly good", "fairly poor", and "poor" prognostic subgroups).

Figure 3: Cumulative/dynamic ROC curves (apparent estimate) for mortality evaluated at 9 months for the final prognostic model, GCS, and MRC Grade in the HIV-uninfected and HIV-infected TBM populations. MRC Grade I (GCS 15; no focal neurological signs); MRC Grade II (GCS 11-14, or 15 with focal neurological signs); MRC Grade III (GCS≤10)).

Figure 4: Nomograms for the prediction of 9-month mortality based on the final prognostic models for the HIV-uninfected and HIV-infected TBM populations, respectively. To derive a prediction, locate the value of each predictor on the corresponding variable line, read the corresponding points assigned on the 0-100 scale and sum all of these points to a total point score. Then read the result on the Total Points scale and its corresponding prediction below. For HIV-infected nomogram, the cohort variable was chosen as the most recent trial [3] since this is most relevant for future prediction.

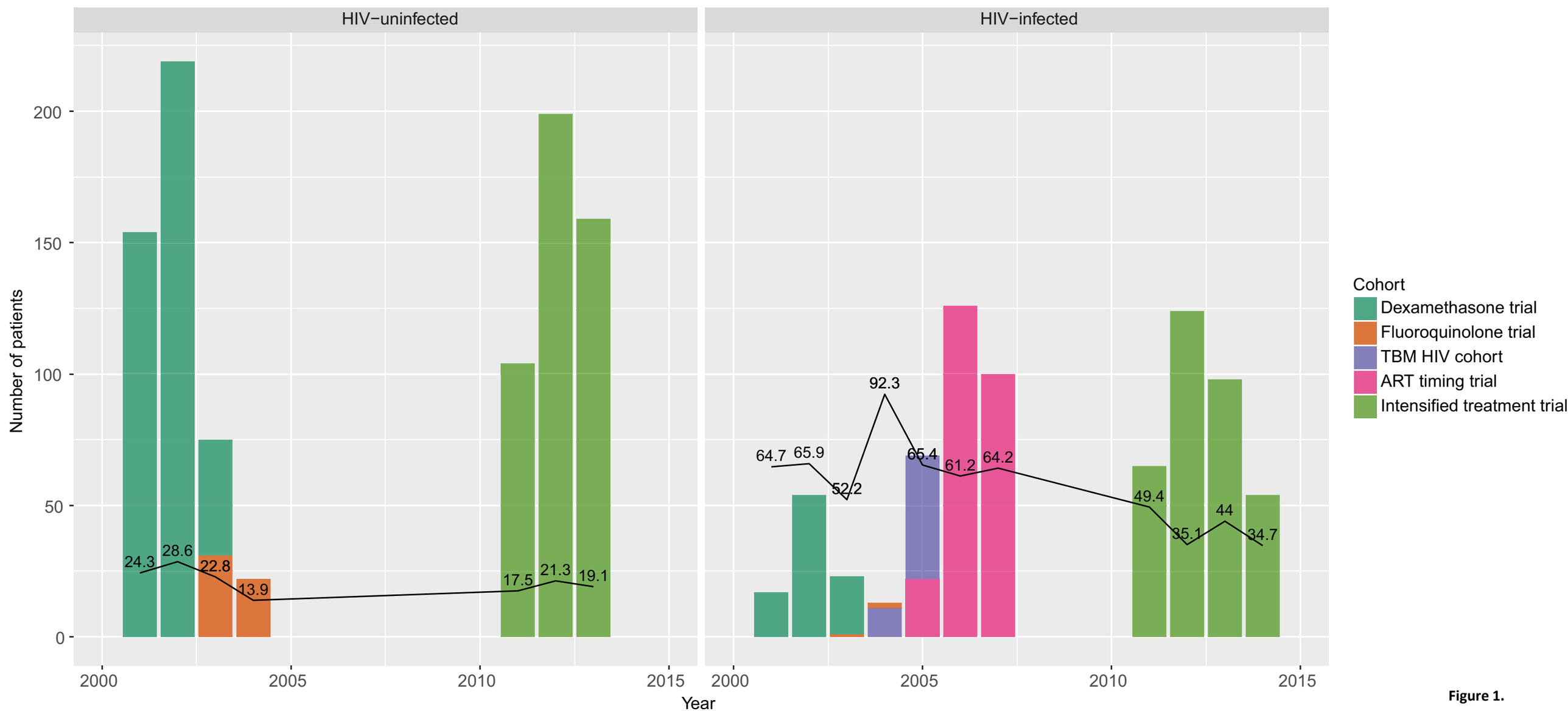
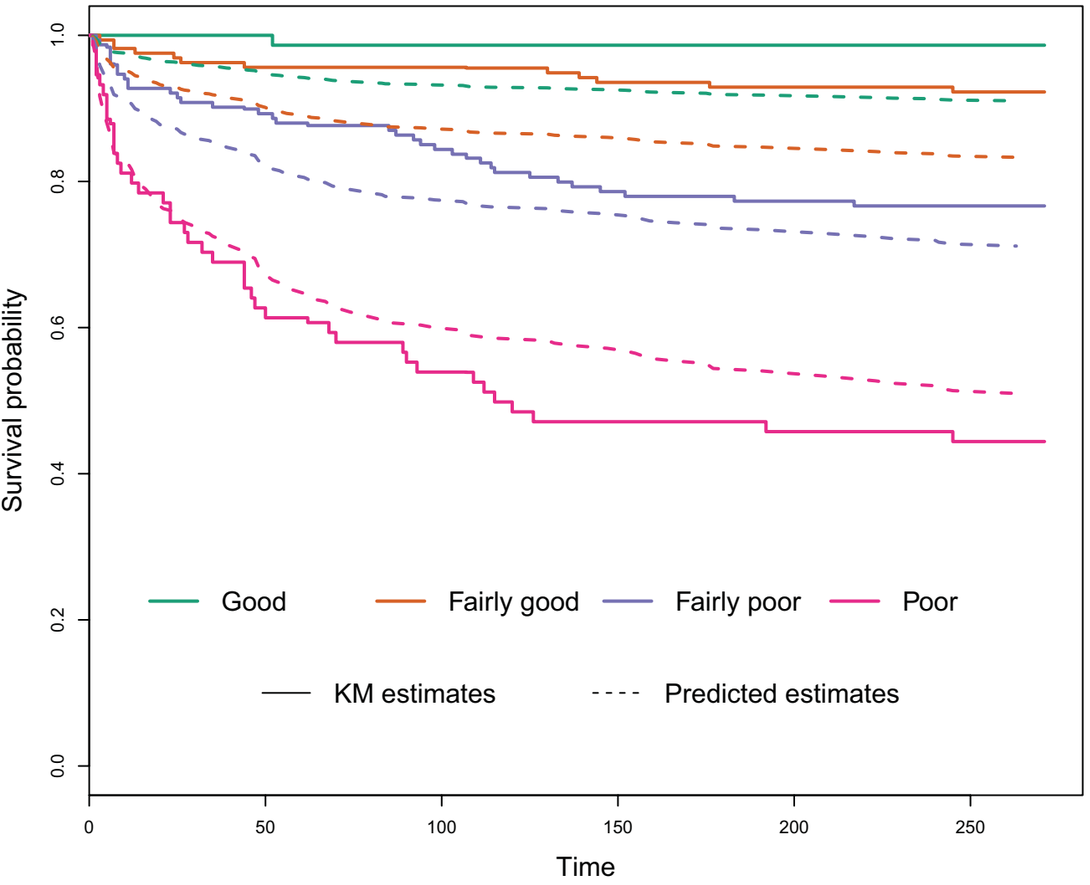
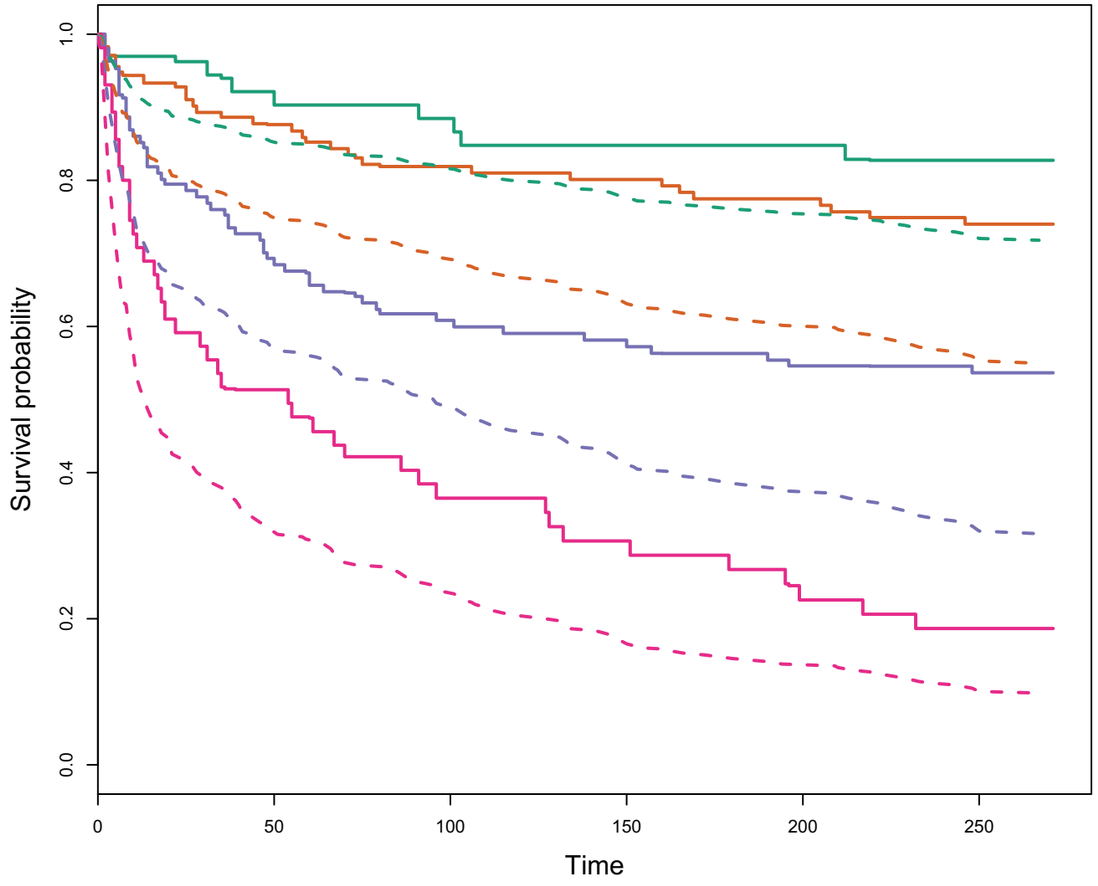

HIV−uninfected
HIV−infected
Number of patients
0
50
100
150
200
2000
2005
2010
2015
Year
24.3
28.6
22.8
13.9
17.5
21.3
19.1
64.7
65.9
52.2
92.3
65.4
61.2
64.2
49.4
35.1
44
34.7
Cohort
Dexamethasone trial
Fluoroquinolone trial
TBM HIV cohort
ART timing trial
Intensified treatment trial

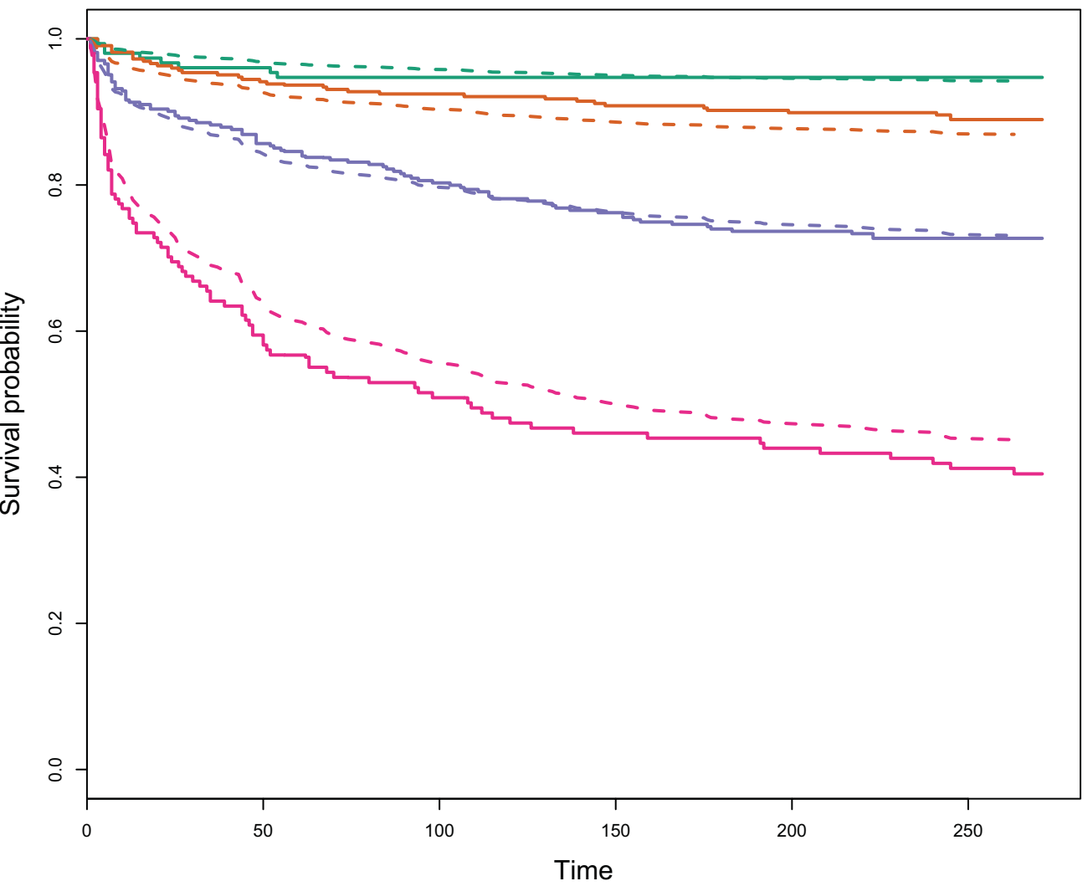
Figure 1.



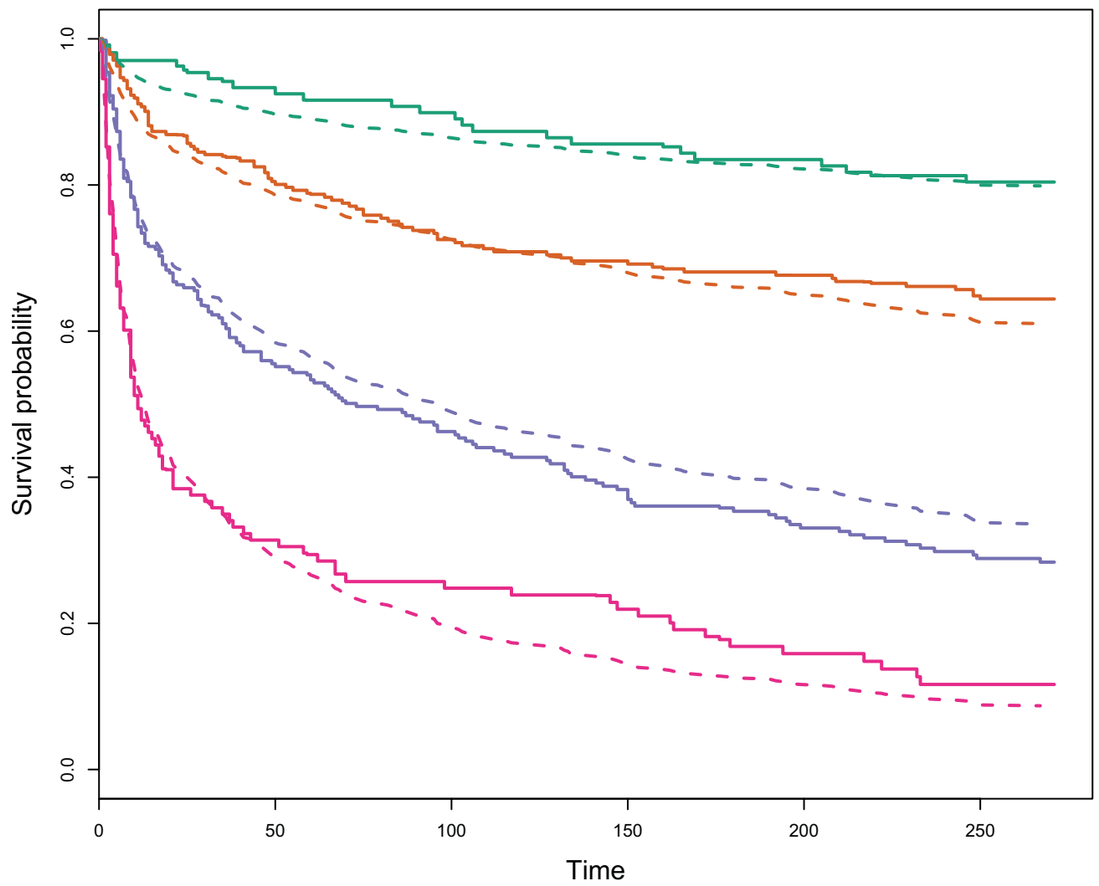
a) HIV-uninfected TBM population, temporal validation



b) HIV-infected TBM population, temporal validation

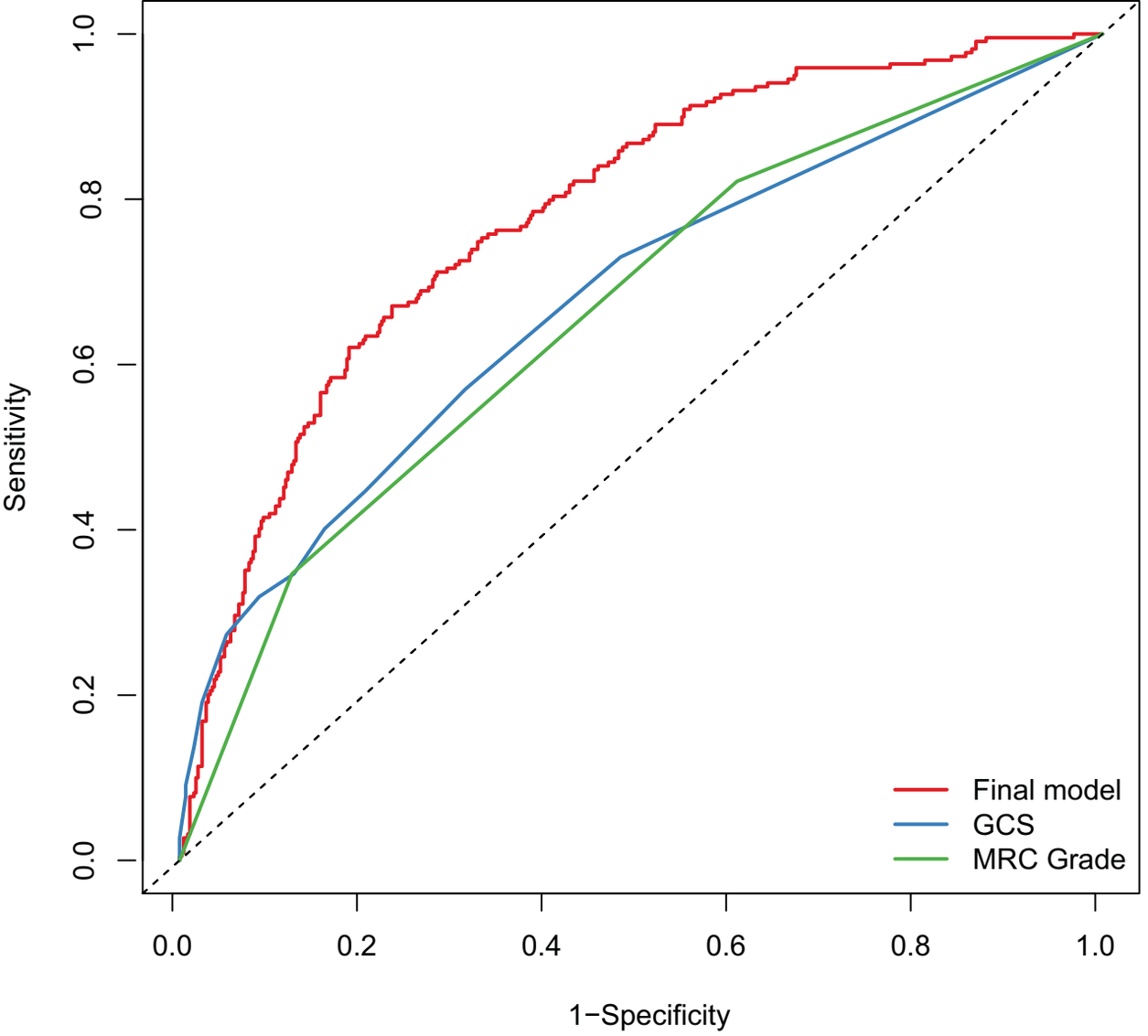


c) HIV-uninfected TBM population, all multiply imputed data

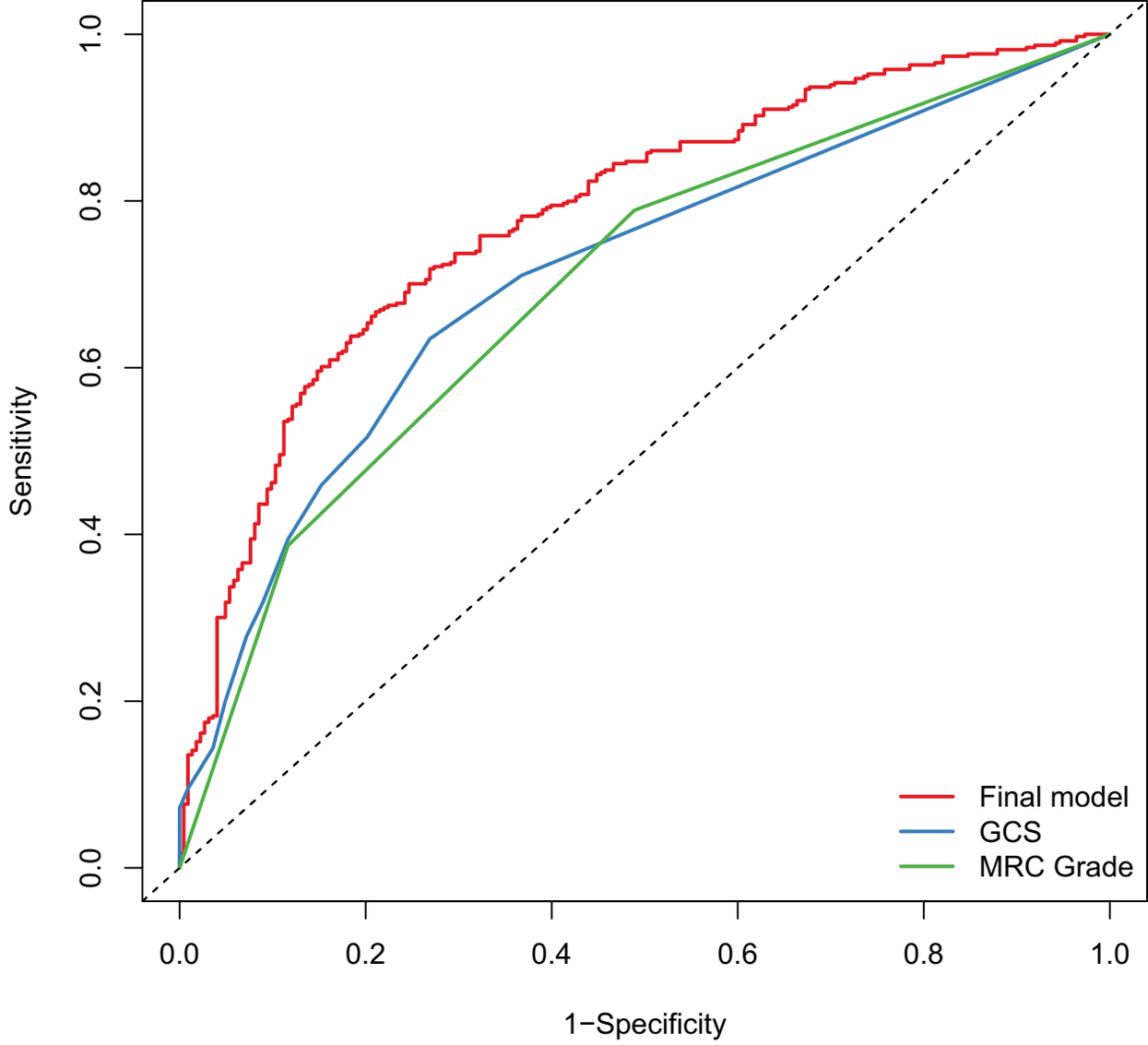


d) HIV-infected TBM population, all multiply imputed data

Figure 2.

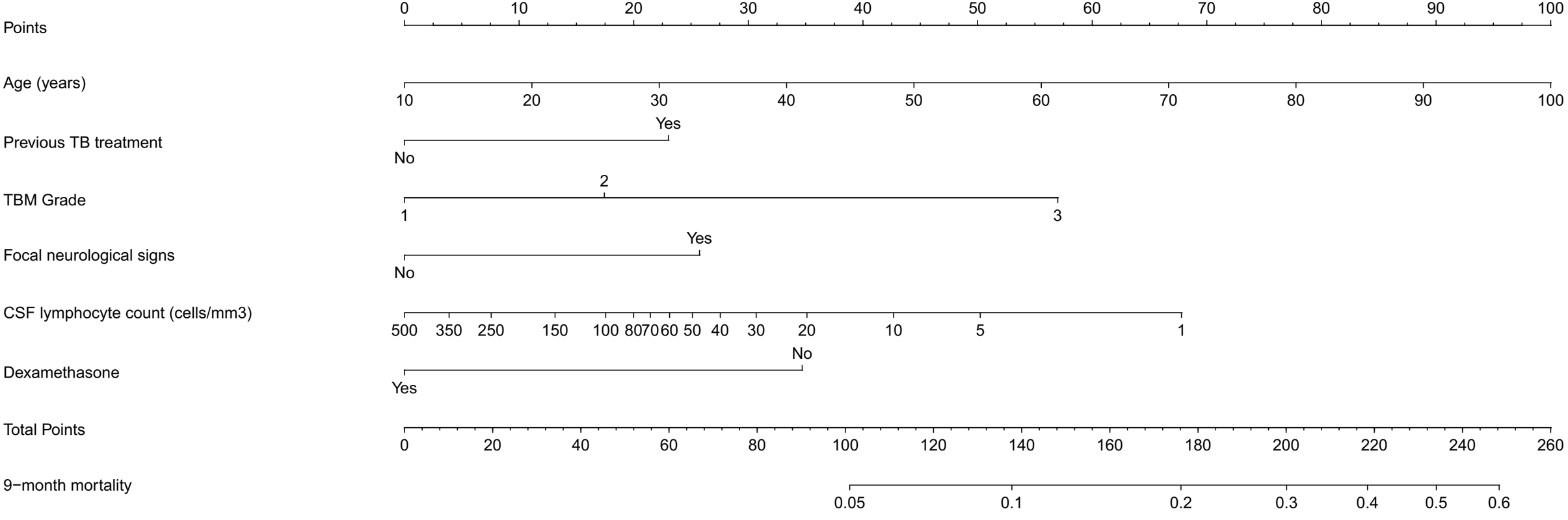


a) HIV-infected TBM population

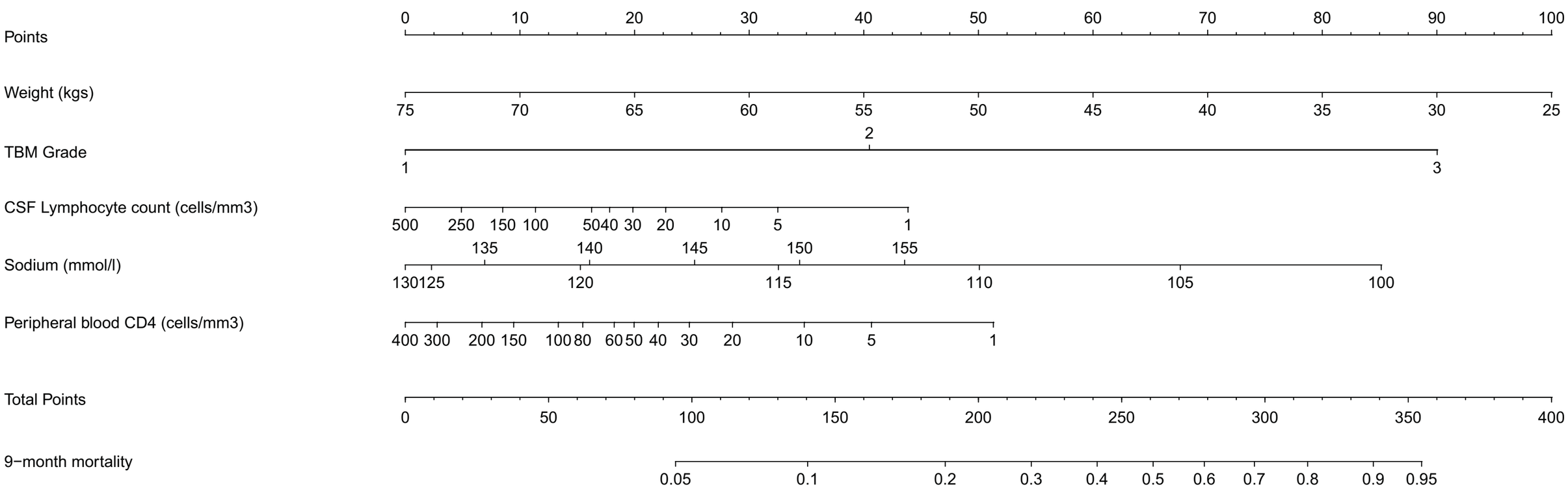


b) HIV-uninfected TBM population

Figure 3.



a) HIV-uninfected TBM population



b) HIV-infected TBM population

Figure 4.